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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
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EXAMINER	
ZEMAN, M	
ART UNIT	PAPER NUMBER
1643	16

DATE MAILED: 02/02/99

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 9/11/98 + 11/17/98 + 12/07/98

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 88-114 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 88-94 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

★ U.S. GPO: 1996-404-496/40517

DETAILED ACTION

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit **1643**.

1. Since this application is eligible for the transitional procedure of 37 CFR 1.129(a), and the fee set forth in 37 CFR 1.17(r) has been timely paid, the finality of the previous Office action is hereby withdrawn pursuant to 37 CFR 1.129(a). Applicant's first submission after final filed on 9/11/98 and the supplemental amendment of 11/17/98 have been entered.

2. Claims 88-114 are pending in the application. Claims 40-87 have been canceled.

3. Applicant's arguments filed 11/17/98 have been fully considered but they are not completely persuasive.

Claim Rejections - 35 USC § 112

4. Claims 89-91 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 89-91 refer specifically to the proteins E1, E2 and an E1/E2 complex. The specification, as filed, fails to set forth these terms and their definition such that it was clear that

applicant had possession of the E1, E2 or E1/E2 complexed proteins at the time of the invention. the specification refers generally to supposed "envelope proteins" and a general area of the polyprotein where they may be, but does not discretely identify the envelope proteins, nor does it give them the names E1, or E2. There is no disclosure in the application as filed, that the envelope protein(s) may form a complex of any kind. Therefore these claims represent new matter and must be canceled in response to this rejection.

5. Claims 88-114 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 88 sets forth a composition comprising a "substantially isolated" polypeptide. The metes and bounds of the term "substantially isolated" are unclear as the degree of purification intended to fall within the scope of the claim is not clearly set forth in the claims or the specification.

In claim 88 the phrase "polypeptide... of an envelope domain of an HCV genome..." is illogical. A polypeptide is not part of a genome, it is encoded by the genome. The HCV genome is made up of nucleic acids, and is therefore not a polypeptide.

Claims 92-95 are improperly dependent from claim 88. Claim 88 states that the polypeptide is selected from the group consisting of an envelope polypeptide of HCV and fragments of that envelope polypeptide. The group does not include core region polypeptides,

NS1 polypeptides, or NS2 polypeptides as claimed in claims 92-95. There is insufficient antecedent basis for these terms in claim 88 from which claims 92-95 depend.

Claim 105 appears to be incomplete, or if complete, fails to further limit the parent claim. Claim 105 states that the "HCV genome hybridizes." All polynucleic acids hybridize to some other polynucleic acid, so this limitation fails to limit the preceding claims. It would appear further limitations to the hybridization were omitted from the claim.

Claims 88, 92-96, and 104 recite "immunogenic polypeptide or fragments" of various HCV proteins. The metes and bounds of the term "fragments" of a polypeptide are unclear, and the specification does not set forth a definition of such immunogenic fragments, such that their meaning is explicit. A fragment of a polypeptide could be one amino acid, however it is unlikely such a fragment would be immunogenic.

6. Claims 88-114 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 88-114 are drawn to immunogenic HCV polypeptides or immunogenic fragments of HCV polypeptides, and methods of using those compositions to provoke an immune response. The specification, as filed, is not enabling for those claims.

The arguments hinge on the definitions of the terms "antigenic" and "immunogenic" and the differences between the two. The specification appears to draw a distinction between the two

terms. The specification defines an immunogenic polypeptide at page 35 as "a polypeptide that elicits a cellular and/or humoral immune response, whether alone or linked to a carrier in the presence or absence of an adjuvant." This definition is without meaning as it has no clear metes and bounds. Virtually any polypeptide linked to a carrier in the presence of an adjuvant will elicit either a cellular or humoral immune response, thus defining a polypeptide as an immunogenic polypeptide appears no different from defining a polypeptide as being a polypeptide. One of ordinary skill in the art might well envision an implied limitation that the response be specific for the polypeptide, however, applicant's arguments at page 9, first paragraph belie even this. An antigenic polypeptide is defined in the specification at pages 27-31 as a polypeptide that comprises an epitope which is immunologically identifiable by or immunologically reactive with a specific antibody. An antigen is not necessarily immunogenic. The ability to be bound by a particular antibody or by patient sera is not necessarily predictive of its ability to provoke an immune response. Sections II B and II C of the specification are entirely devoted to "antigenic" polypeptide production and linkage to a carrier, while II E requires "immunogenic" polypeptides. So it is clear that the differences between the terms "antigenic" and immunogenic" were well appreciated by Applicant at the time of filing.

Applicant argues that the specification is "replete with examples of immunogenic polypeptides" but this is simply not the case. The specification details the production of several antigenic polypeptides, and many potential antigenic sequences, but fails to set forth any teaching or guidance as to whether or not any of these polypeptides is or would be immunogenic, i.e.

would provoke any kind of immune response upon administration to a host. Section II E which discusses immunogenic polypeptides does not refer to any particular regions, sequences or areas of HCV which would be immunogenic, and the entire section is prophetic in nature, setting forth potential lines of experimentation which can be followed in the future. None of the antigens identified in the specification was tested for its immunogenicity (C100, NANB5-1-1 etc.).

Applicant has submitted the declaration of Dr Weiner part of which is directed to this rejection. Dr Weiner states that methods of testing a polypeptide for its immunogenicity were known in the art at the time of the invention. This statement is not in dispute. What is at issue is whether the specification provides enough guidance as ho how to identify immunogenic polypeptides of HCV such that they could be tested in such a known manner. It is the Examiner's position that it does not. The specification devotes much description to the definition of an antigenic polypeptide, the epitope it comprises, and how it is identified, and examples of antigenic polypeptides. Immunogenicity of those polypeptides is not discussed. The specification does not set forth what defining characteristics much be present in a polypeptide for it to be immunogenic, nor does it point to examples of immunogenic HCV sequences. The specification does not draw a link between a polypeptide's antigenicity and it's immunogenicity, in fact, it clearly separates the definitions of the two. Dr Weiner's declaration asserts that it would have been obvious to try to identify immunogenic polypeptides of HCV sequences, however given the lack of guidance as to how to identify immunogenic regions of the enormous polyprotein of HCV one of ordinary skill in

the art would not have had a reasonable expectation of success of finding such immunogenic regions without undue experimentation.

Further, the specification does not offer a written description of any immunogenic polypeptides of HCV, or immunogenic fragments of those polypeptides. Legal precedent dictates that conception of a chemical compound, such as a DNA molecule, or polypeptide sequence, is not achieved until reduction to practice has occurred. (*Amgen Inc v. Chugai Pharmaceutical Co. Ltd* 18 USPQ2d 1016-1031 (CAFC 1991); *Fiers v. Revel* 25 USPQ2d 1601-1607 (CAFC 1993)). At no point in the specification are particular immunogenic polypeptides or immunogenic fragments of HCV polypeptides disclosed. In *Amgen Inc v. Chugai Pharmaceuticals Co. Ltd* 18 USPQ2d 1016 (CAFC 1993) the court ruled that:

> Conception of a chemical compound requires that inventor be able to define compound so as to distinguish it from other materials, and to describe how to obtain it, rather than simply defining it solely by its principal biological property; thus, when inventor of gene, which is chemical compound albeit complex one, is unable to envision detailed constitution of gene so as to distinguish it from other materials, as well as method for obtaining it, conception is not achieved until after gene has been isolated.

The court further elaborated on this point and concluded that:

> A gene is a chemical compound, albeit a complex one, and it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it. *See Oka*, 849 F2d at 583 7 USPQ2d at 1171. Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its methods of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by its principal biological property, e.g., encoding human erythropoetin, because an alleged conception having no more specificity

> than that is simply a wish to know the identity of any material with that biological property. We hold that when an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the gene has been isolated. (emphasis added)

Applicant has pointed to recitations in the specification indicating that immunogenic regions of HCV could exist, and could be identified, however, those regions or sequences were not identified. These arguments are analogous to the above recited "wish to know the identity" of those other immunogenic polypeptides of HCV.

The significance of conception and reduction to practice was further addressed by the court in *Fiers v. Revel* 25 USPQ2d 1601-1607 (CAFC 1993):

> Conception is question of law, reviewed de novo on appeal, and if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated; thus, regardless of complexity or simplicity of method of isolation employed, conception of DNA sequence, like conception of any chemical substance, requires definition of that substance other than by its functional utility. (emphasis added)

In the instant application, Applicants have identified antigenic polypeptides of HCV. The immunogenicity, as defined by Applicant, of any polypeptides made from the disclosed HCV sequences is not addressed in the specification. As argued by Applicant, the sequence of HCV was previously unknown and one would not have been able to predict the immunogenicity of any HCV proteins at the time the invention was made.

Even if one concedes for arguments sake that it does not require undue experimentation to obtain immunogenic fragments it remains that one is not taught how to use any fragment made. One is not taught how to use an immunogenic fragment by reference to a catalog of potential uses, such a catalog merely sets forth additional experimental challenges to discover the use. Moreover, immunogenicity in one species does not necessarily reflect immunogenicity in other species. Having in hand immunogenic polypeptides permits one to test for those which could confer protective immunity, however, there is no predictability as to which one, if any, will elicit protective immunity.

Nowhere in the specification are the proteins of HCV described or isolated. The claims embrace the proteins which naturally occur as part of the virion, however, the specification fails to set forth their isolation as well as failing to set forth how to isolate the virus. Nor can one infer what proteins are present in the virion from the presumptive polyprotein as HCV is neither a flavivirus nor a togavirus.

Claim Rejections - 35 USC § 102

Claims 88-99 and 111-114 are drawn to compositions comprising substantially isolated HCV polypeptides, and methods for their use. The language of the claims does not exclude the presence of other polypeptides, and even reads on intact partially purified virus.

Applicant has submitted the declaration of Dr Weiner which is in part directed to the art rejections below. Dr Weiner asserts that the agents identified by Bradley, He or Prince may not be HCV, but applicant's assertions are not supported by evidence of any differences. The Office

does not have the facilities to test the agents of Bradley, He or Prince with the agent of the invention. In regard to Bradley in particular, Dr Weiner disputes the identity of one of the agents of Bradley, yet is silent in regards to the other agent. In regards to He, Dr Weiner suggests other viral agents may have been present in the preparation of He, but provides no evidence to that effect. In regard to Prince, Dr Weiner does not dispute that the viral preparation is HCV, but argues that Prince does not set forth substantially isolated peptides of HCV. As set forth above, the claims are not so limited.

7. Claims 88-99 and 111-114 remain rejected under 35 U.S.C. 102(b) as being anticipated by Bradley.

Bradley (Bradley 1985 J Virological Methods 10 p307-319) discloses several purified or isolated NANBV agents, which are infectious, and produce NANBH in chimpanzees. One is a concentrated fraction of Factor VIII, both unpassaged, and passaged twice through chimpanzees. Bradley also discusses the "F" strain and the "H" strain, both isolated by Feinstone, and infectious. The "H" strain was later identified as HCV, and is also variously called the Hutchinson strain (see Ogata et al. 1991 PNAS USA 88 p 3392-3396). All of these viral preparations comprise at least 8 amino acids of HCV sequence, and provoke an immune response.

8. Claims 88-99 and 111-114 remain rejected under 35 U.S.C. 102(b) as being anticipated by He.

He (He et al. 1987 J Infectious Diseases 136 (4) p 636) discloses purified preparations of the "H" strain of HCV, also known as the Hutchinson strain. He sizes the H strain virions

through filtration. The filtered virus was still infectious. He indicates that flaviviruses are among the types of viruses that would be of the size collected in the infectious filtered sample. This purified fraction comprises a polypeptide having at least 8 contiguous amino acids of HCV, and is able to provoke an immune response upon immunization, or infection with that fraction.

9. Claims 88-99 and 111-114 remain rejected under 35 U.S.C. 102(b) as being anticipated by Prince.

Prince (Prince et al. J Medical Virology 16 p119-125) discloses a method of inactivating the Hutchinson strain of HCV. One sample of the Hutchinson strain is sterilized by treatment with beta-propiolactone and UV light. The treated sample was non-infectious. The untreated sample was infectious. This control inoculum of the Hutchinson strain of HCV comprises an immunogenic HCV polypeptide having at least 8 nucleotides of an HCV sequence.

Conclusion

10. No Claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mary K Zeman whose telephone number is (703) 305-7133. The examiner can be reached between the hours of 7:30 am and 5:00 pm Monday through Thursday, and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Chris Eisenschenk, can be reached on (703) 308-0452.

The fax number for this Art Unit is (703) 305-7401.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

mkz
January 31, 1999

MICHAEL P. WOODWARD
PRIMARY EXAMINER
TC 1600